RESEARCH NEWS AND TRENDS FROM THE NATIONAL INSTITUTE ON DRUG ABUSE

NIDA Notes

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Studies Link Family of Genes to Nicotine Addiction

Genes for protein constituents of nicotinic acetylcholine receptors influence early smoking responses and the likelihood of nicotine dependence.

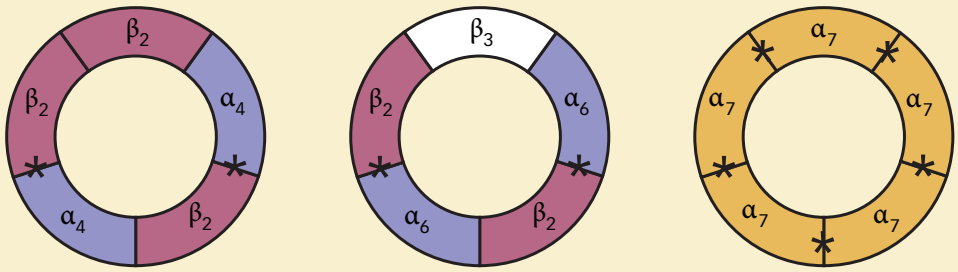
BY LORI WHITTEN,
NIDA Notes Staff Writer

One person reaches for a cigarette soon after waking, smokes a pack a day, and cannot seem to quit. Another smokes a few cigarettes now and then but never feels driven by the need for nicotine. A third person smoked for a while in youth and then stopped. According to several recent NIDA-funded studies, such contrasting smoking patterns and responses may arise because individuals inherit different forms of half a dozen genes that dictate the features of the brain receptor to which nicotine binds.

Scientists have long known that nicotine produces many of its effects by attaching to receptors for acetylcholine, a neurochemical that influences memory, arousal, attention, and mood. These nicotinic acetylcholine (nACh) receptors comprise five subunits arranged around a central pore, like sections of an orange. Each of the genes identified by the new studies provides the blueprint for one of a dozen proteins, labeled $\alpha_{2\text{-}10}$ and $\beta_{2\text{-}4}$, that serve as subunits in nACh receptors. Variations in the DNA that encodes these genes may alter the structure or amount of the proteins produced, which in turn can modify what happens when nicotine molecules attach to the receptors.

[*Continued on page 10*]

NICOTINIC RECEPTORS VARY IN COMPONENT PROTEINS AND ACTIVITY Nicotine initiates its effects by binding to nicotinic acetylcholine (nACh) receptors, each consisting of five proteins arranged in a circle around a central pore. The receptors occur in subtypes, which differ in their constituent proteins and physiological and pharmacological characteristics. Asterisks indicate where nicotine and acetylcholine bind to each receptor subtype.



$\alpha_4\beta_2$: The most common and best-studied subtype

$\alpha_6\beta_2\beta_3$: A subtype localized to a few brain areas

α_7: A subtype containing just one kind of subunit

ALSO IN THIS ISSUE

By NORA D. VOLKOW, M.D., *NIDA Director*

NIDA's 35th Anniversary: Science Focused on Solutions

Congress created the National Institute on Drug Abuse in 1974 to bring the power of science to bear against a burgeoning epidemic of drug abuse and addiction. The wisdom of that decision is evident in today's roster of proven effective interventions to prevent and treat addiction and in the increased public understanding that addiction is a chronic brain disease rather than a moral failure.

Since its inception, NIDA has funded and guided a comprehensive program of basic and clinical research involving many of the Nation's premier scientists and clinicians. Our goal is to apply the fruits of scientific discovery to real-world problems. Our mission also includes informing the Nation about the nature and dangers of drug abuse and addiction.

Among their major accomplishments, NIDA-supported researchers have

- Established and maintained national data collection systems to monitor patterns of drug abuse and identify population groups at risk.
- Showed that all abused and addictive substances share certain neural and molecular effects. These findings and others on the particular effects of specific drugs led to the development of medications to treat opioid and nicotine addiction.
- Identified principles of successful drug abuse prevention.
- Advanced effective drug abuse treatments based on biological, developmental, social, and environmental factors.
- Demonstrated that drug abuse treatment can reduce the spread of HIV and support effective treatment of HIV disease.
- Applied genetics, epigenetics, and neuroimaging techniques to the study of drug abuse, opening up extraordinary opportunities for the development of new and increasingly individualized approaches to prevention and treatment.

Drug abuse evolves constantly as new drugs and new patterns of abuse emerge, each with new consequences for public health. In its 35 years, NIDA has responded to epidemics of cocaine, methamphetamine, and steroid abuse, as well as drugs' contributions to the spread of HIV and hepatitis C. Today, NIDA-funded researchers are seeking answers to the emergence of marijuana of unprecedented potency, rising prescription drug abuse, and the impact of combat stress on veterans' risk of drug involvement. In the future, as now and in the past, NIDA will engage each new challenge with comprehensive scientific strategies and the most advanced scientific tools and technologies to alleviate the impact of drugs on the health and prosperity of affected individuals, their families and communities, and the Nation. ■

NIDA Notes

EDITOR
David Anderson
Public Health Advisor, Office of Science Policy and Communications, National Institute on Drug Abuse

DEPUTY EDITOR
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DESIGN/LAYOUT
Maggie Bray
MasiMax Resources, Inc.

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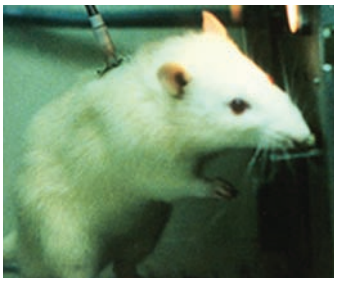


Rats Reared Alone Show ADHD Signs

Laboratory animals raised in isolation may provide useful subjects for studies of attention-deficit hyperactivity disorder (ADHD) and other conditions characterized by impulsive choice. Dr. Jennifer Perry of the Minneapolis Medical Research Foundation and Dr. Michael Bardo of the University of Kentucky found that rats make more impulsive choices after being raised alone in bare laboratory cages than when raised in group housing equipped with novel objects. Treating rats from the two contrasting environments with medications for ADHD produced results parallel to those seen in people with and without ADHD: Injections of the ADHD medications d-amphetamine or methylphenidate moderated the excess impulsivity of the animals reared alone. In contrast, among animals reared in the enriched environment, the drugs did not decrease impulsive choice, and d-amphetamine actually increased that trait. The researchers plan to use rats raised in isolation to explore the neurobiology that links impulsivity and vulnerability to addiction.

> Behavioural Brain Research 193(1):48–54, 2008.

Anticipation of Methadone Enhances Brain Reactivity to Heroin Cues

Images of heroin preparation and injection can incite craving and excite brain areas associated with reward-seeking even in stabilized, long-term, methadone-maintained patients, according to Drs. Daniel Langleben, Anna Rose Childress, Charles O'Brien, and colleagues at the Penn-VA Addiction Treatment Research Center at the University of Pennsylvania School of Medicine and McLean Hospital, Harvard University. The research team used functional magnetic resonance imaging to monitor activity in the extended limbic system of 25 patients in long-term methadone maintenance while showing them heroin-related images before and after their daily methadone dose. Subjective heroin craving and limbic reactivity to heroin cues were greater before, as compared with after, the daily methadone medication, but methadone plasma levels were uncorrelated with the brain response. The findings suggest that individuals in methadone maintenance treatment remain responsive to cues that may motivate heroin seeking and relapse, particularly under conditions of high drug expectancy, such as prior to their daily medication dose.

> American Journal of Psychiatry 165(3):390–394, 2008.

Recovery May Be Harder for Adolescents, Animal Study Suggests

Adolescents' heightened sensitivity to drug reward puts them at enhanced risk for progressing from drug experimentation to addiction and may also increase their challenges in recovery. In a recent experiment, researchers taught rats to associate a specific site with cocaine infusions. After dispensing of the drug was halted, adolescent rats continued to return to the site for 9 days; adult rats, in comparison, stopped frequenting the site after 5 days. The finding confirms that adolescents experience cocaine's rewarding effects more intensely and suggests that they develop cocaine–environment associations that are harder to break, say Drs. Heather Brenhouse and Susan Andersen of McLean Hospital, Harvard Medical School, in Boston.

The adolescent animals in the experiment also renewed their predilection for the cocaine-associated site more readily than the adults when given a priming mini-dose of the drug. One potential implication, the researchers say, is that adolescent drug abusers may need longer treatment interventions than adults do to achieve stable recovery.

> Behavioral Neuroscience 122(2):460–465, 2008.

Test Substance Attenuates Signs of Cocaine Withdrawal in Rats

An experimental compound that selectively stimulates delta opioid receptors reduces anxiety- and depression-like behaviors that follow cessation of chronic cocaine exposure in rats. Dr. Ellen Unterwald of Temple University School of Medicine and The Rockefeller University tested the compound, SNC80, after she, Dr. Shane Perrine, and colleagues discovered that delta opioid receptors in the rat brain do not respond effectively after chronic cocaine exposure. Other researchers had linked decreased delta opioid receptor responsiveness with rodent behavior resembling human anxiety and depression.

Two FDA-approved medications, propranolol and amantadine, have also shown potential to ease these cocaine withdrawal symptoms in clinical trials. Propranolol appears to blunt anxiety by blocking the receptor for adrenaline, a hormone released during stressful situations. Amantadine seems to boost mood by increasing levels of dopamine and norepinephrine in the brain. Treatment of the anxiety and depression that frequently accompany withdrawal from cocaine is important because it reduces the rate of relapse to cocaine addiction.

> Neuropharmacology 54(2):355–364, 2008.

Recovery Checkup System Helps Substance Abusers Who Have Mental Disorders

Benefits include quicker return to treatment when recovery falters and longer retention.

BY LORI WHITTEN,
NIDA Notes Staff Writer

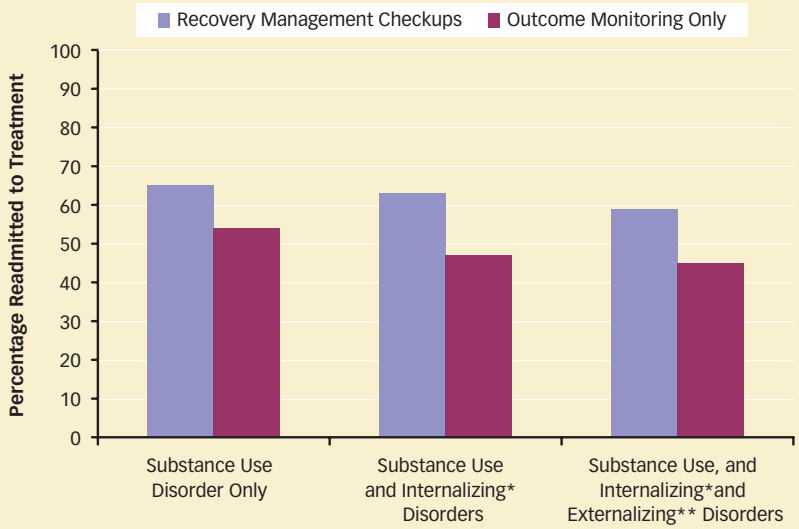
A posttreatment intervention to support recovery may be especially beneficial for substance abusers with co-occurring mental disorders. In a recent subgroup analysis of data from previous trials, Dr. Michael Dennis and Dr. Christy Scott of Chestnut Health Systems in Chicago and Dr. Brian Rush of the Centre for Addiction and Mental Health in Toronto, Canada, found that clients with co-occurring disorders responded to the intervention with improvements on more measures than did substance abusers without other mental health problems.

Recovery management checkups (RMC) aim to identify and alleviate client problems before they derail recovery and to facilitate rapid readmission to treatment when recovery falters. Quarterly appointments form the core of RMC. During these sessions, interviewers assess clients using the structured Global Appraisal of Individual Needs tool and refer those with significant problems to a linkage manager, who administers a brief intervention using motivational interviewing techniques. The linkage manager connects clients who are willing to appropriate community resources, including admission to a treatment program, and continues to work with them until they have been engaged in treatment for at least 2 weeks. The conceptual framework of RMC is to treat addiction as a chronic disease, with long-term management to minimize the number of acute episodes of substance abuse and with prompt treatment when episodes occur to prevent them from becoming more severe and consequential.

The new analysis included 865 people who were recruited as they entered substance abuse treatment at the Haymarket Center in Chicago. Over 66 percent of the participants met past-year criteria for one or more co-occurring mental disorders, including 27 percent with only internalizing disorders (e.g., mood, anxiety, and trauma disorders) and 39 percent with both internalizing and externalizing disorders (e.g., attention, hyperactivity, impulse, conduct, and gambling disorders). Among the three groups, the likelihood of having a history of substance abuse treatment, of mental health treatment, and of a wide range of other problems, such as homelessness and victimization, was lowest in the participants with substance use disorder only and highest in those with substance abuse and both internalizing and externalizing mental disorders. In the latter group, 76 percent of the participants reported having been homeless at some time, and 91 percent reported having been victimized.

The study protocol assigned the participants to receive intensive outpatient

RECOVERY MANAGEMENT CHECKUP SYSTEM BENEFITS SUBSTANCE ABUSERS WITH MENTAL DISORDERS More patients who participated in quarterly Recovery Management Checkups returned to treatment upon relapse than those who received assessments only. The enhanced-checkup intervention benefited substance abusers whether or not they had mental disorders.



* Mood, Anxiety, and Trauma Disorders.
** Attention, Hyperactivity, Impulse, Conduct, and Gambling Disorders.

therapy, short- or long-term residential therapy, or detoxification, as deemed appropriate based on their initial presentation. The study protocol scheduled all participants for quarterly visits to a clinic, beginning 90 days after their pretreatment interview and assessment and continuing for 2 years. Patients randomized to RMC received support from the linkage manager if they needed treatment, while patients randomized to control were only assessed, although they could re-enter treatment on their own.

Among all three comorbidity subgroups—those with only substance abuse, those with substance abuse and at least one internalizing disorder, and those with substance abuse and internalizing and externalizing disorders—more than 80 percent were assessed as needing to return to treatment at least once over the 2-year study. Consistent with the goals of RMC, more participants who received the intervention returned to treatment, and they returned sooner. Overall, 59 percent of the RMC group returned to treatment, as compared with 45 percent of the other group, and their average time before treatment was 306 days, as compared with 630 days. The sizes of these differences were similar across all the comorbidity subgroups.

On some additional outcomes, only RMC recipients with mental disorders showed a benefit. For example, RMC recipients with an internalizing disorder spent at least 40 more days in treatment than controls with those problems. Among patients with both an internalizing and an externalizing disorder, those who received RMC were abstinent on 51 more days than controls during the study and demonstrated an unmet need for treatment at nearly one-third fewer of their visits.

CONCRETE LONG-TERM SUPPORT

For most substance abusers—and especially those with co-occurring mental health problems—addiction is a chronic, relapsing condition. "Our recovery management checkup system addresses that reality, and it's good to see that the intervention helps an important subgroup of patients—those with co-occurring mental disorders—as well as others," Dr. Dennis says.

"Decisionmakers need data to convince them that RMC can work with patients who have the most severe problems, and our findings are a good first step in that direction," adds Dr. Rush. The researchers plan to verify their results by following part of the cohort for an additional 2 years. The Chestnut team also plans to test RMC with women leaving the criminal justice system in Chicago, and Dr. Rush has proposed developing an RMC system in Canada.

"The RMC intervention offers a recovery-oriented approach," says Dr. Thomas Hilton of NIDA's Division of Epidemiology, Services and Prevention Research. "It not only monitors substance abuse after treatment but also assesses the characteristics, or recovery capital, that facilitate a healthy, productive, drug-free lifestyle in the long term. Knowing each patient's recovery capital is critical because recovery occurs outside the direct care system and rests heavily on the shoulders of the individual. It makes good clinical sense to build up the patient's capacity for recovery if it is low, and the RMC offers a concrete intervention that provides support." ■

SOURCE

Rush, B.R. et al. The interaction of co-occurring mental disorders and recovery management checkups on substance abuse treatment participation and recovery. *Evaluation Review* 32(1):7–38, 2008.

Study Gives Green Light to Antiretroviral Medications for HIV-Infected Injection Drug Users

HIV mortality rates were similar regardless of whether patients used illicit injection drugs.

BY LORI WHITTEN,
NIDA Notes Staff Writer

Limited access, financial constraints, and stigma—rather than lifestyle—may be the main obstacles keeping HIV-infected injection drug users from obtaining the benefit of highly active antiretroviral therapy (HAART). In a prospective study in a setting of universally guaranteed health care, including free medications for the indigent, mortality rates from HIV in infected people who used illicit injection drugs and those who did not use injection drugs were nearly identical over the 5 years following HAART initiation.

In 2006, 205,000 injection drug users were living with HIV in the United States, according to the Centers for Disease Control and Prevention. Although HAART is not a cure, it improves the prognosis for people infected with the virus. However, past studies have shown that physicians tend not to recommend HAART when a patient has a history of injection drug use. Some doctors assume that injection drug users will be unable to adhere to HAART's stringent medication regimens or that liver disease, which is common among injection drug users, might impede the medications' therapeutic efficacy. The new results counter those concerns and indicate that access to HAART can improve the health of HIV-infected patients who have a history of injection drug use.

MONITORING PATIENT MORTALITY

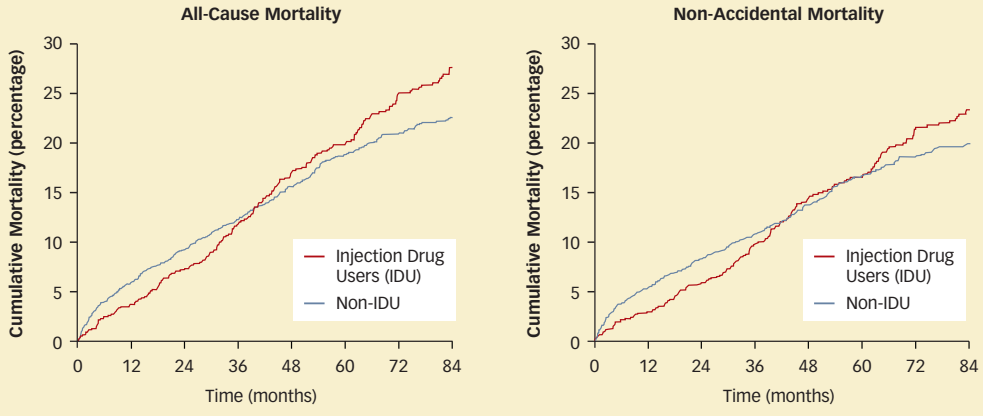
In their study, Dr. Evan Wood of the British Columbia Center for Excellence in HIV/AIDS and colleagues enrolled everyone who started HAART therapy in British Columbia, Canada, between August 1996 and June 2006. Of these 3,116 men and women, 915 used injection drugs. At the time they initiated anti-HIV therapy, both the injection drug users and the other patients averaged about 40 years of age and, as citizens of Canada, had access to free medical care and HAART.

Dr. Wood and colleagues followed the participants until June 30, 2007—a span of 5.3 years on average for the patients who used injection drugs and 4.3 years for the other patients. During the first year on HAART, 41 percent of the patients using injection drugs took 95 percent or more of their medications on schedule, as compared with 63 percent of the other patients. Nevertheless, the two groups' cumulative mortality rates, 27 percent and 22 percent, respectively, did not differ meaningfully at any point. These rates yielded an estimate that the drug injectors' risk of dying was 1.09 times that of the other patients—a difference well within the range that is potentially attributable to chance. The relative risk estimate narrowed further, to 1.06, when the researchers excluded from their analysis 87 deaths—caused by accidental poisonings, suicides, and trauma (see graph)—that were clearly unrelated to the HIV disease process. Although the two groups' mortality rates appeared to be diverging at the end of the followup period, the data demonstrated a clear clinical benefit of making HAART available to patients who use injection drugs.

"Potent antiretroviral therapies equally benefited people with and without injection drug use, despite the lower medication adherence among people who had used injection drugs," says Dr. Wood. "HAART not only benefits the health of

[*Continued on page 9*]

INJECTION DRUG USERS BENEFIT FROM HAART In British Columbia, where everyone has full access to HIV care and medications, injection drug users' all-cause and HIV-related survival rates did not differ from those of other patients throughout 7 years following initiation of highly active antiretroviral therapy (HAART).



Rare Glutamate Receptor Proliferates After Cocaine Withdrawal

Molecular change in rat brains parallels increase in drug-seeking behavior.

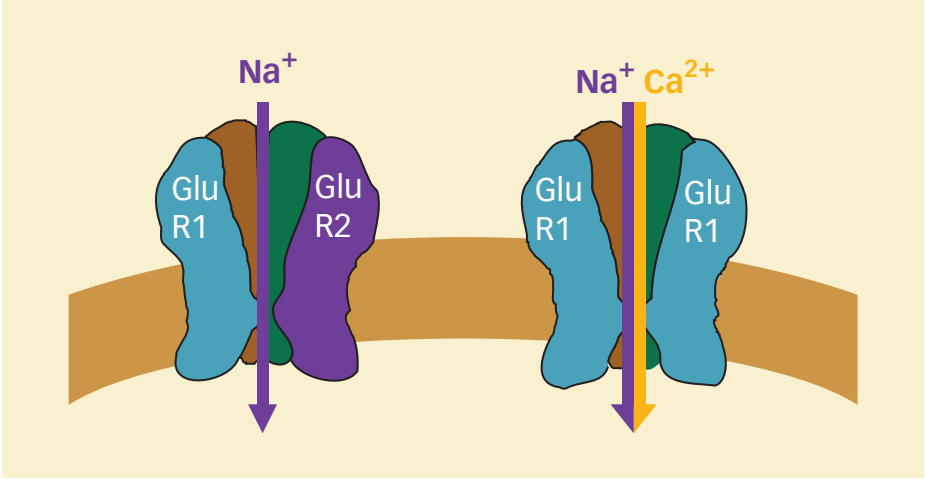
BY MOLLY MCELROY,
NIDA Notes Contributing Writer

Proliferation of a rare neuroreceptor may underlie the intensification of craving that cocaine abusers experience during their first weeks of abstinence. NIDA-funded researchers found that, in rats, the quantity of these receptors in the nucleus accumbens (NAc) increased from the first to the 45th drug-free day and correlated with an increase in the animals' drug-seeking.

The implicated receptors are a subtype of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor. AMPA receptors regulate cellular responses to the neurotransmitter glutamate throughout the brain, including in the NAc, an area that shapes motivation by linking experience to feelings of reward and satisfaction. Most AMPA receptors include subunits called GluR1 and GluR2, but those newly generated following cocaine withdrawal lack GluR2.

"Switches in the subunit composition of AMPA receptors have been uncovered in other neural modifications, but our study describes the most long-lasting change that has yet been found in any brain region," says Dr. Marina Wolf of the Chicago Medical School at Rosalind Franklin University of Medicine and Science. According to Dr. Wolf, her team's results are particularly exciting because they show how long-lasting modifications can be produced in the adult brain and because the brain alteration is directly linked to a disease-related behavioral change.

NEW RECEPTORS APPEAR DURING WITHDRAWAL FROM COCAINE
AMPA receptors respond to glutamate signals within the brain and play a role in cocaine seeking. These receptors have four subunits that typically include one called GluR2 (left). However, during withdrawal from cocaine, new AMPA receptors that lack GluR2 (right) appear in the membranes of nerve cells in the brain's nucleus accumbens. The new receptors are more permeable to calcium and have a higher ion flow when activated than the more common AMPA receptors.



NOSE POKES AND RECEPTORS

Scientists have long recognized that cocaine craving intensifies, or incubates, for several weeks following withdrawal from the drug. Cocaine abusers' reports of craving and their risk of relapse both peak after several weeks of abstinence.

Prior NIDA-funded research has shown that drug craving involves a complex neuronal circuit that includes cortical and limbic regions, as well as NAc. However, there is evidence that glutamate inputs into the NAc are part of a final common pathway for drug seeking. What's more, AMPA-type glutamate receptors are increasingly recognized as key players in the rewiring of brain circuits in response to many kinds of experience. Dr. Wolf's team therefore focused on testing the role of NAc AMPA receptors in the incubation of cocaine craving.

The team's first step was to induce craving incubation in rats. Animals were trained to poke their noses into a hole in a test chamber to elicit an intravenous infusion of cocaine. Each infusion was paired with a light or light-plus-tone cue, enabling the rats to learn to associate these cues with cocaine availability. Rats had access to cocaine for 6 hours a day, enabling a high level of drug intake. After 10 days of this regimen, the researchers initiated cocaine withdrawal by halting the rats' access to the drug.

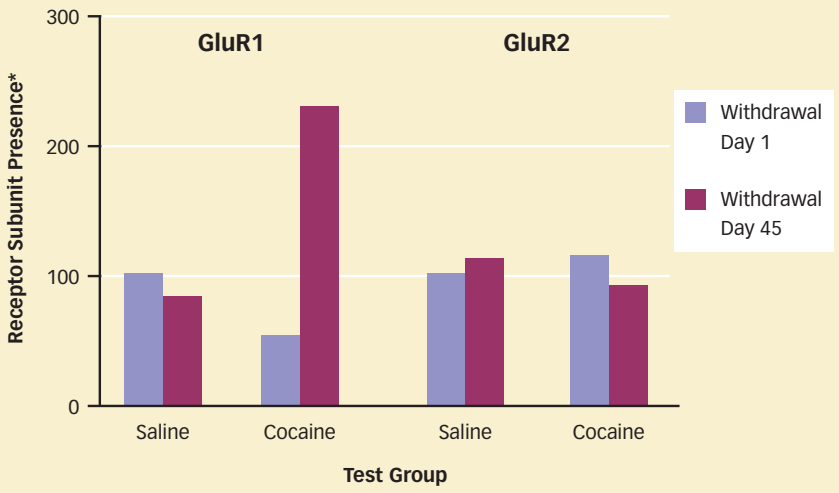
At intervals during the rats' withdrawal from the drug, the researchers returned them to the test chamber. The rats resumed poking their noses in the hole, but the poking now brought no cocaine.

The researchers counted the number of nose pokes as a measure of the animals' desire for the drug and the willingness to expend effort to obtain it. The rats poked more than twice as much on withdrawal day 45 than on withdrawal day 1, demonstrating that their urge to obtain cocaine had increased—incubated—during the interval.

Biochemical assays of the rats' brain tissue showed that the number of GluR1 receptor subunits in the NAc doubled between withdrawal day 1 and day 45. There was no concomitant increase in GluR2 subunits, however, indicating that the NAc cells had generated a new complement of GluR2-lacking receptors during this interval. No other brain area exhibited AMPA changes, nor were there changes in another common type of glutamate receptor, the NMDA receptor.

The researchers next established a causative role for the newly formed GluR2-lacking AMPA glutamate receptors in the rats' drug-seeking behavior. They injected a chemical (1-naphthyl acetyl spermine, or NASPM) that prevents glutamate from binding to GluR2-lacking AMPA glutamate receptors into the NAc of cocaine-exposed rats and showed that, in this situation, incubation is inhibited. Derived from a spider toxin, the chemical reduced cocaine-seeking behavior on withdrawal day 45 by more than half.

AMPA RECEPTORS PRODUCED DURING COCAINE WITHDRAWAL LACK GLUR2 SUBUNITS Between day 1 and day 45 of cocaine withdrawal, the number of GluR1 receptor subunits increased dramatically, while the number of GluR2 subunits stayed about the same.



* Expressed as percentage of level measured for the saline control on day 1 of withdrawal.

MECHANISMS OF INCUBATION

The new findings may be explained in terms of previous research that has shown that what happens when glutamate binds to an AMPA receptor depends, in part, on whether the receptor contains GluR2. All AMPA receptors contain an ion channel that allows sodium entry, which excites neurons by depolarizing them. AMPA receptors that lack GluR2 admit calcium as well as sodium. This leads to a stronger depolarization as well as other consequences for intracellular signaling.

"Calcium entry through the GluR2-lacking AMPA receptor channel may contribute to cocaine-induced brain changes by activating signaling pathways that are not in play when other types of AMPA receptors are stimulated in normal rats," Dr. Wolf suggests. For example, calcium influx into brain cells via glutamate receptors has been shown to promote lasting sensitization of the cell to future glutamate signals in a process, called long-term potentiation, that encodes information and experience during learning. Such sensitization in the NAc, with its role in motivation and reward, would be compatible with incubation of cocaine craving and seeking.

Why should cocaine withdrawal precipitate AMPA receptor proliferation in the NAc? Dr. Wolf and colleagues note that during cocaine withdrawal, areas of the brain that release glutamate into the NAc are hypoactive. Possibly, the NAc ramps up its AMPA receptor complement to compensate for the resulting reduction in incoming neurotransmitter.

"This compensatory change backfires when the animal encounters a cocaine-related cue and glutamate is released into the NAc," says Dr. Wolf. "This occurs because the responsiveness of the NAc neurons to glutamate has been increased due to synaptic incorporation of GluR2-lacking AMPA receptors. We propose that this enhanced responsiveness of NAc neurons underlies increased cue-induced cocaine craving."

CLINICAL APPLICATIONS

In recovering addicts, exposure to environmental cues previously associated with drug use, such as cocaine paraphernalia, is an important trigger for cocaine craving leading to relapse. Dr. Wolf's work on cue-induced cocaine craving in rats suggests that GluR2-lacking AMPA glutamate receptors might be a useful target for medications designed to reduce the frequency of relapse. While blocking glutamate receptors may lead to serious side effects, selective blockade of GluR2-lacking AMPA receptors might be less problematic because these receptors are a minority population in the normal brain,

according to Dr. Wolf.

NASPM cannot be used in people because it works only when injected directly into the brain. Scientists may, however, develop similar blockers in the future that could be taken as pills or by injection. Such a medication might be used to dampen cue-induced cocaine craving during the first few months of withdrawal, when abstinent cocaine addicts are particularly prone to cue-induced relapse, Dr. Wolf says.

Dr. Jerry Frankenheim of NIDA's Functional Neuroscience Research Branch agrees that a drug that acts like NASPM could potentially be a useful treatment for blocking cue-induced cocaine seeking. "NIDA's medications development group is also looking into NASPM as a lead towards a therapy to prevent relapse," he says.

He adds that NASPM-like compounds may be useful for other cue-induced drug cravings as well as in treating brain disorders, including neuronal cell death and epilepsy.

"The expression of GluR2 in neurons is altered not only by drugs of abuse but also, in certain vulnerable neurons, after seizures, ischemia, or administration of some other drugs. For example, in some neurons, ischemia triggers down-regulation of GluR2 and enhances AMPA receptor-mediated calcium and zinc influx that may mediate the death of these neurons. Therefore, NASPM-like medications may obtain several therapeutic applications," Dr. Frankenheim says.

"Dr. Wolf's work represents part of an exemplary, synergistic collaboration with members of NIDA's Intramural Research Program, including Dr. Yavin Shaham, who in 2001 first reported incubation of cocaine craving in an animal model," says Dr. Frankenheim. ■

SOURCE

Conrad, K.L. et al. Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. *Nature* 454(7200): 118–121, 2008.

■ ANTIRETROVIRAL MEDICATIONS

[*Continued from page 6*]

individuals, but it may also reduce the transmission of HIV to others." The team plans to examine whether, by lowering viral load, HAART can decrease the number of new transmissions from both injection drug users and people who do not inject drugs.

"Approximately one-third of HIV infections outside sub-Saharan Africa are attributable to injection drug use, according to the Joint United Nations Programme on HIV/AIDS," says Dr. Jacques Normand, director of NIDA's AIDS Research Program. "Because HAART has produced dramatic improvements in HIV patients' survival and may reduce transmission of the virus, increasing HAART delivery to injection drug users should be a global public health priority." ■

SOURCE

Wood, E. et al. Highly active antiretroviral therapy and survival in HIV-infected injection drug users. *JAMA* 300(5):550–554, 2008.

RECEPTOR LINK TO NICOTINE ADDICTION

[*Continued from page 1*]

Initially, research examining the influence of nACh receptor proteins on nicotine addiction focused on the α_4 and β_2 subunits. These are the most abundant and widely distributed nACh subunit proteins in the brain. Animal and human imaging studies have shown that nACh receptors consisting of two α_4 and three β_2 subunits are critical for the rewarding effects of nicotine.

The new studies highlight genes that code for less common nACh receptor proteins (see table, p. 11). Researchers have implicated the genes—located on chromosome 15—for the α_3, α_5, and β_4 proteins in early initiation of smoking, the transition to dependence, and two smoking-related diseases: lung cancer and peripheral arterial disease. Investigators have also found that whether or not a person experiences extreme dizziness upon first trying cigarettes, as well as his or her risk of addiction, depends in part on the genes—on chromosome 8—for the α_6 and β_3 proteins. Taken together, the results suggest that genes for several nACh receptor proteins drive different aspects of the multistep process of nicotine addiction.

FIRST RESPONSES TO SMOKING

A study led by Dr. Marissa A. Ehringer at the University of Colorado examined responses of more than 1,000 17- to 21-year-olds who had been asked to recall their initial responses to smoking. All the youths had smoked almost every day for at least one month at some time, but not all had continued smoking or had become addicted to nicotine. The researchers compared the youths' reports with analysis of their DNA, focusing on the gene for the β_3 protein and specifically on seven small variations called single nucleotide polymorphisms (SNPs) that produce alternate forms, or alleles, of the gene in some individuals.

For four of the β_3 SNPs, the allele that the youths possessed correlated with their initial responses to smoking, which could have included nausea, dizziness, positive feelings such as mellowness or increased energy, or negative feelings such as depression or anxiety.

The researchers looked again at two of these β_3 SNPs in a followup study of a separate sample of approximately 2,500 subjects, including some sibling pairs. This complementary analysis also found evidence that these four β_3 SNPs shape individuals' initial smoking responses, particularly feelings of dizziness, relaxation, or "pleasurable buzz." The followup also pointed to similar effects of one SNP in the gene for the α_6 protein. More recently, the Colorado researchers, in collaboration with Dr. Laura Jean Bierut's team at Washington University in St. Louis, found an association between β_3 SNPs and early response to nicotine in a third sample.

Dr Ehringer and colleagues found that the same α_6 and β_3 SNPs that correlated with initial responses to smoking also correlated with nicotine dependence in adults.

Laboratory Studies Link Receptor Subtypes to Nicotine Withdrawal

Researchers are also conducting experiments with genetically engineered animals to investigate the roles of nACh proteins on smoking responses. NIDA-funded researchers Dr. M. Imad Damaj and colleagues at Virginia Commonwealth University recently showed that mice whose genes for various nACh subunit proteins had been deleted exhibited altered profiles of nicotine withdrawal. For example, removing the gene for the β_2 protein reduced expressions of anxiety and aversion without affecting other signs of withdrawal; animals lacking the gene for the α_7 protein, in contrast, demonstrated less hypersensitivity to pain; and deletion of the α_5 protein resulted in fewer paw tremors and backing movements, which are considered to be physical signs of nicotine withdrawal. Overall, the findings suggest that the β_2 nicotinic acetylcholine receptor protein contributes to the negative emotions triggered by nicotine withdrawal, while the α_5 and α_7 proteins underpin specific bodily signs of the withdrawal process. More recent research by Dr. Damaj and colleagues suggests that the α_6 protein influences nicotine reward and negative emotions triggered by nicotine withdrawal but not acute nicotine-induced physical signs of the withdrawal process.

SOURCES

Jackson, K.J. et al. The role of α-containing nicotinic acetylcholine receptors in nicotine reward and withdrawal. *The Journal of Pharmacology and Experimental Therapeutics* 331(2):547–54, 2009.

Jackson, K.J. et al. Differential role of nicotinic acetylcholine receptor subunits in physical and affective nicotine withdrawal signs. *The Journal of Pharmacology and Experimental Therapeutics* 325(1):302–312, 2008.

Dr. Ehringer hypothesizes that the intensity of early smoking experiences may be as important as their character—either pleasant or unpleasant—in determining whether someone continues to use nicotine after initial experimentation. For example, dizziness is not a sensation that people generally enjoy, yet reporting intense dizziness after the first few cigarettes is associated with nicotine dependence in adulthood.

In another project, the Colorado team tested for associations between the genes on a region of chromosome 15 that code for three nACh receptor proteins—α_3, α_5, and β_4—and individuals' experiences with smoking and alcohol. Their initial study with youths and a larger, more focused study with adults both linked three SNPs—one in the α_5 gene, one in the β_4 gene, and one located between these genes—to the age at which individuals had begun using both substances. For each of these SNPs, one allele was associated with having first smoked and consumed alcohol sooner and the other with having done so later. Dr. Ehringer and colleagues hypothesize that genes in this region confer vulnerability to problematic risk-taking, a character trait that affects the age at which people begin smoking.

"Our results suggest that, once an individual begins smoking, this [α_3] allele predisposes him or her to smoke heavily and find it difficult to stop."

—Dr. Kári Stefánsson

A genetic influence on the age of smoking initiation, such as Dr. Ehringer has identified, may have public health consequences: Studies have indicated that the younger people are when they first light up, the more likely they are to become addicted. This may be particularly true for individuals who inherit certain alleles of the gene for the α_5 protein, according to Dr. Robert B. Weiss and colleagues at the University of Utah School of Medicine.

Searching for links between the genes for the α_3, α_5, and β_4 proteins and the severity of nicotine dependence, these researchers collected smoking histories, diagnostic assessments, and DNA from over 2,800 European-American long-term smokers. The researchers found several SNPs in the α_5 gene whose alternate alleles corresponded to different levels of risk for severe nicotine dependence. But the correspondence held only among people who started smoking daily before age 16. Dr. Weiss suggests that people with

DEVELOPMENT OF AN ADDICTION Recent studies link genes for subunits of the nicotinic acetylcholine receptor to early smoking, initial responses to tobacco smoke, and vulnerability to addiction.

Aspect of Smoking	Subunit Gene(s)	Type of Study	Participants	Researchers
Dizziness from first cigarette	β_3	Gene association*	1,075 adolescent smokers and nonsmokers	Marissa A. Ehringer et al.
Pleasure from initial cigarette	α_5	Gene association*	435 adult smokers	Laura Jean Bierut, Ovide Pomerleau, Richard Sherva, et al.
Age of smoking initiation	α_5, β_4	Gene association*	1,075 adolescent smokers and nonsmokers	M. A. Ehringer et al.
Increased risk of dependence among early smokers	α_5	Candidate-gene**	2,827 long-term smokers	Robert B. Weiss et al.
Transition to dependence	β_3	Genome-wide association***	1,929 smokers, Collaborative Genetic Study of Nicotine Dependence	L.J. Bierut, Scott Saccone, et al.
Transition to dependence	α_3, α_5, β_3	Candidate-gene**	1,929 smokers, Collaborative Genetic Study of Nicotine Dependence	L.J. Bierut, S. Saccone, et al.
Transition to dependence	α_5	Genome-wide association***	Approximately 15,000 adults	Wade Berrettini et al.
Transition to dependence	α_3	Genome-wide association***	Approximately 14,000 smokers, 16,000 nonsmokers	Kári Stefánsson et al.
Lung cancer and peripheral arterial disease	α_3	Genome-wide association***	Approximately 14,000 smokers, 16,000 nonsmokers	K. Stefánsson et al.

* Links genes with smoking by comparing the genetic markers of participants with and without the condition.
** Compares genes, selected on the basis of a demonstrated or hypothesized link, from individuals with and without the condition.
*** Considers genetic markers across the entire genome to compare participants with and without the condition.

the higher risk alleles of these SNPs may especially benefit from early smoking prevention interventions.

A recent study linked another aspect of risk with one of the α_5 SNPs associated with nicotine dependence in the Weiss study. Drs. Bierut, Ovide Pomerleau, and colleagues found that regular smokers who had the higher-risk allele were more likely to recollect having had a pleasurable response the first time they smoked.

FROM THE FIRST CIGARETTE TO ADDICTION

Drs. Bierut, Scott Saccone, and colleagues found that the genes for the α_5 and β_3 nACh receptor proteins affect an individual's risk of progressing from casual smoking to addiction. The 1,900 individuals who contributed DNA to their study had each smoked at least 100 cigarettes in their lifetime; about half were moderately to severely dependent on nicotine, while the others had not developed dependence on the drug, according to the Fagerstrom Test for Nicotine Dependence. The researchers looked for correlations between these divergent smoking histories and 4,000 SNPs within 348 genes that previous research had linked to nicotine

Genes Newly Linked to Nicotine Dependence

Smoking addiction commences when nicotine binds to nicotinic acetylcholine receptors, but the process ultimately involves proteins that participate in a wide variety of neuronal functions. A recent study by Dr. Laura Jean Bierut and colleagues at Washington University in St. Louis suggests that several genes that code for basic brain functions may influence an individual's vulnerability to nicotine's addictive effects.

The genome-wide association study compared the genetic profiles of a group of smokers with moderate to severe nicotine dependence to those of another group whose members had consumed at least 100 cigarettes but had not become nicotine–dependent. Out of thousands of small genetic variations examined, several were linked to genes associated with nicotine dependence. One was within a gene, called *VPS13A,* that helps determine which proteins should be broken down and eliminated by the waste disposal organelles inside cells. A second small variation associated with nicotine dependence was within a gene called *CTNNNA3,* which other researchers have linked with levels of plasma amyloid beta protein in Alzheimer's disease.

Two genes associated with calcium channels, which control the response of cells to stimulation, were also highlighted:

- *CLCA,* which encodes the protein that forms the calcium channel in lungs and which other research has linked to chronic obstructive pulmonary disease.
- *TRPC7,* which earlier work had associated with maintenance of calcium channels and with nicotine-induced behavior in roundworms.

The St. Louis researchers also corroborated a suspected association between nicotine dependence and the gene *NRXN1*. This gene provides the blueprint for one of a family of proteins, called the neurexins, that influence neurotransmitter release and other aspects of cell-to-cell communication. Prior research by other teams had linked genes in this family to other addictions (see "New Technique Links 89 Genes to Drug Dependence," *NIDA Notes*, Volume 22, Number 1). More recently, a NIDA-funded team led by Dr. Ming Li at the University of Virginia linked variants of the *NRXN1* gene to nicotine dependence in 2,000 people from 600 families.

"This is a good start toward identifying new genes related to nicotine dependence, and the next step is to validate these findings in an independent data set and then determine what these genes may contribute to nicotine dependence," says Dr. Bierut. "The findings of our genome-wide association study, for example, point to novel biological pathways for nicotine addiction and prompt us to think of its neurobiology in a different way."

SOURCES

Nussbaum, J. et al. Significant association of the neurexin-1 gene *(NRXN1)* with nicotine dependence in European- and African-American smokers. *Human Molecular Genetics* 17(11):1569–1577, 2008.

Bierut, L.J. et al. Novel genes identified in a high-density genome wide association study for nicotine dependence. *Human Molecular Genetics* 16(1):24–35, 2007.

dependence. The strongest associations were with five SNPs: two in the gene for the α_3 nACh receptor subunit, two in the β_3 subunit gene, and one in the α_5 subunit gene. One of the α_5 alleles carried double the risk of its alternative allele.

The trial participants who were not dependent on nicotine were unusually resistant to the drug's addictive effects, Dr. Bierut says. These are smokers who can quit at any time. Identifying the ways that the trial participants' genetic makeup protected them, even past the 100-cigarette threshold, could provide powerful clues to prevention and treatment.

"Our findings point to a role for the α_3 and α_5 proteins, as well as β_4, in nicotine dependence," says Dr. Bierut. "The α_5 proteins are expressed in the brain's reward areas, which makes our findings particularly intriguing."

Dr. Saccone says, "We are very excited to discover that genes encoding nicotinic acetylcholine receptor proteins confer risk for nicotine dependence because they have strong biological relevance to the addiction. My colleagues and I are using samples of DNA from different groups of people to confirm these findings; the next step is to determine exactly how alleles of these genes cause someone to keep smoking." Both St. Louis studies also found a link between the gene for the β_3 protein—which was highlighted in the results of the Colorado studies—and nicotine dependence, bolstering confidence in this gene's involvement in the addiction.

Other researchers have corroborated and extended the St. Louis team's findings. For example, Dr. Wade Berrettini and colleagues at the University of Pennsylvania found that SNPs in the gene for the α_5 protein influence the risk of smoking a pack of cigarettes a day as compared with smoking fewer than 5 cigarettes a day. A study led by Dr. Kári Stefánsson of deCODE Genetics, a biopharmaceutical company based in Reykjavik, Iceland, also implicated an α_3 gene SNP that influences nicotine dependence but not smoking initiation. Both of these studies employed genome-wide association (GWA) scan methodology, which analyzes hundreds of thousands of SNPs simultaneously. Although GWA scans sometimes produce spurious associations, the convergence of these results with those of the St. Louis group provides strong evidence for the positive findings.

"Once scientists determine how these genetic variants affect nicotinic receptor function and behavioral responses to nicotine, they can develop pharmacotherapy interventions."

—Dr. David Shurtleff

SMOKING-RELATED DISEASES

The Icelandic study included nearly 14,000 smokers, a sample large enough to detect relationships between genes and long-term smoking outcomes of lung cancer and peripheral arterial disease. Among these Caucasian European men and women, the same α_3 allele that promotes dependence also accounted for 18 percent of lung cancer cases and 10 percent of peripheral arterial disease cases.

"Our results suggest that, once an individual begins smoking, this allele predisposes him or her to smoke heavily and find it difficult to stop," says Dr. Stefánsson. It may also influence other aspects of smoking, he adds, such as vulnerability to harmful effects of smoking or depth of inhalation. "These traits would affect the risk for lung cancer and peripheral arterial disease, erasing the line that people have traditionally drawn between environmental and genetic contributions," he says.

Two studies by researchers at the University of Texas in Houston and the International Agency for Research on Cancer in Lyon, France, also found that the α_3 variant increases risk for lung cancer. These researchers, however, disagree with Dr. Stefánsson's explanation for the link; they argue that the variant increases cancer risk via mechanisms independent of nicotine addiction.

FROM GENE DISCOVERY TO TREATMENT

The SNPs identified in these studies may themselves affect nACh responses to nicotine by altering the form of their product proteins or their patterns of expression in different regions of the nervous system. Alternatively, further investigations may reveal that some of the SNPs are genetic bystanders that correlate with smoking behaviors only because they are inherited along with nearby, as yet unidentified DNA variants. Scientists plan to sort through these possibilities, pinpointing which alleles affect receptor responses to nicotine singly and which work in concert with others and determining how those altered responses promote or protect against nicotine addiction. A similar agenda applies to research on several genes that code for proteins that are unrelated to the nACh receptor but have recently been linked to addiction (see box, page 12).

"Once scientists determine how these

genetic variants affect nicotinic receptor function and behavioral responses to nicotine, they can develop pharmacotherapy interventions," says Dr. David Shurtleff of NIDA's Division of Basic Neuroscience and Behavioral Research. "Of the nicotinic receptors identified as novel targets in these studies, the α_5 protein stands out. It seems to influence severe nicotine addiction," he says.

NIDA geneticist Dr. Joni Rutter agrees that the α_5 receptor, in particular, is an interesting target. "This protein is not as abundant in the brain as other nicotinic receptor subtypes, so medications that target it might have few side effects and higher efficacies," she adds.

For people who have a genetic predisposition to various aspects of smoking addiction, the solution is simple, says Dr. Stefánsson. "It is only smoking that converts the risk into addiction and disease," he notes. "The ultimate preventive measure for these conditions is to never start smoking." ■

SOURCES

Ehringer, M.A. et al. Association of CHRN genes with "dizziness" to tobacco. *American Journal of Medical Genetics. Part B Neuropsychiatric Genetics* [Epub ahead of print, September 16, 2009].

Berrettini, W. et al. Alpha-5/alpha-3 nicotinic receptor subunit alleles increase risk for heavy smoking. *Molecular Psychiatry* 13(4):368–373, 2008.

Hoft, N.R. et al. Genetic association of the CHRNA6 and CHRNB3 genes with tobacco dependence in a nationally representative sample. *Neuropsychopharmacology* 34(3):698–706, 2008.

Schlaepfer, I.R. et al. The CHRNA5/A3/B4 gene cluster variability as an important determinant of early alcohol and tobacco initiation in young adults. *Biological Psychiatry* 63(11):1039–1046, 2008.

Sherva, R. et al. Association of a single nucleotide polymorphism in neuronal acetylcholine receptor subunit alpha 5 (CHRNA5) with smoking status and with "pleasurable buzz" during early experimentation with smoking. *Addiction* 103(9):1544–1552, 2008.

Thorgeirsson, T.E. et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature* 452(7187):638–642, 2008.

Weiss, R.B. et al. A candidate gene approach identifies the CHRNA5-A3-B4 region as a risk factor for age-dependent nicotine addiction. *PLoS Genetics* 4(7):e1000125, 2008.

Zeiger, J.S. et al. The neuronal nicotinic receptor subunit genes (CHRNA6 and CHRNB3) are associated with subjective responses to tobacco. *Human Molecular Genetics* 17(5):724–734, 2008.

Bierut, L.J. et al. Novel genes identified in a high-density genome wide association study for nicotine dependence. *Human Molecular Genetics* 16(1):24–35, 2007.

Saccone, S.F. et al. Cholinergic nicotinic receptor genes implicated in a nicotine dependence association study targeting 348 candidate genes with 3713 SNPs. *Human Molecular Genetics* 16(1):36–49, 2007.

Program Aims to Expand Physician Training to Treat Drug Addiction

Physicians in all areas of medical practice—not just those already specializing in addiction—can receive certification to treat drug addiction under a new program the American Board of Addiction Medicine (ABAM) is establishing.

"We want addiction prevention, screening, intervention, and treatment to become routine aspects of medical care, available virtually any place health care is provided," says ABAM President Dr. Kevin Kunz.

ABAM was founded in 2007 to set standards for educating physicians in addiction medicine, to certify primary care practitioners and a wide range of medical specialists to treat addiction, and to require and track continuing education in addiction treatment. A major focus of the program is the creation of accredited addiction residency programs in medical schools and hospitals across the Nation.

Dr. Kunz says he believes that within 3 to 7 years, "a 1- to 2-year residency will be mandatory for those seeking certification in addiction medicine." He says ABAM is establishing a framework for model residencies that meet the criteria of the Accreditation Council for Graduate Medical Education, the group that accredits postgraduate medical training programs in the United States. ABAM will also seek recognition for the field of addiction medicine by the American Board of Medical Specialties.

For a limited time, physicians who meet certain criteria can become ABAM-certified without completing all the training requirements that will eventually be established. These include some 4,500 physicians who have been certified by examination by the American Society of Addiction Medicine. They can apply for "grandfathering" until December 31, 2009. Thereafter, physicians who are certified in a nonaddiction specialty and meet certain other criteria can receive ABAM certification by taking an exam, scheduled for December 11, 2010.

Further information on ABAM and the exam are available at *www.ABAM.net*.

Substance Abuse and Sexual Risk Show Town-Gown Divide

Two recent studies found differences in behavior between young adults attending college and their peers. Dr. Carlos Blanco of Columbia University in New York and colleagues report that in 2001–2002, one fifth of the Nation's college students had met the clinical criteria for a diagnosis of alcohol abuse disorder within the past 12 months, compared with 17 percent of their noncollege peers. In contrast, drug and nicotine dependencies were more common among nonstudents (7 percent versus 5 percent; 21 percent versus 15 percent). The researchers based their estimates on data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), the largest nationally representative survey of substance abuse and mental health disorders to include college-age students and their noncollege peers. Their analysis linked the difference in alcohol abuse rates to sociodemographic factors that differentially affected the two groups and to recent stressful life events. Fewer than 10 percent of the survey participants with drug or alcohol problems reported having utilized treatment resources, and only half as many college as noncollege individuals reported doing so. The researchers say that their findings, reported in the *Archives of General Psychiatry*, highlight the need for more alcohol abuse screening and intervention, especially on college campuses.

In a survey of 834 youths, college freshmen reported lower rates of risky sexual behavior 6 months after high school graduation than same-age youth who were not attending college. About 23 percent of the college students reported inconsistent condom use during the past month, compared with 35 percent of their noncollege peers; 15 percent said they had engaged in casual sex during the same period (versus 29 percent), and 5 percent reported high-risk sex (versus 16 percent). Jennifer A. Bailey of the University of Washington in Seattle and colleagues report in the *Journal of Adolescent Health* that the college students had lower rates "largely because they were more likely to do well in school and less likely to use drugs and to engage in sexual risk behaviors during high school." Prevention efforts in high school "should result in reductions in the prevalence of risky sexual behaviors in the transition to adulthood," they conclude.

SOURCES

Archives of General Psychiatry 65(12):1429–1437, 2008. *Journal of Adolescent Health* 42(6):573–579, 2008.

Recognition for *NIDA Notes* Science Writing

NIDA Notes received first place in Science Writing in the 2009 Blue Pencil & Gold Screen Awards Competition of the National Association of Government Communicators (NAGC). The award, which recognized the article, "Basic Science Discoveries Yield Novel Approaches to Analgesia" (*NIDA Notes,* Vol. 22, No. 1, p. 1), named Senior Science Writer Lori Whitten, Managing Editor Andrew Keegan, Deputy Editor Julie Ann Miller, and Editor David Anderson. NAGC is a network of professionals who disseminate information on behalf of Federal, State, and local governments. The association's annual awards "salute superior communications efforts of government agencies." ■

VOLUME 22 INDEX

Issue number appears in parentheses, followed by page number(s).

Report Discusses Co-Occurrence of Drug Abuse and Other Mental Disorders

Many individuals who abuse drugs also have other mental disorders. NIDA's latest *Research Report* describes the co-occurrence, or comorbidity, of substance use disorders and other psychiatric disorders such as attention–deficit hyperactivity disorder (ADHD), schizophrenia, and depression.

Drug addiction is a brain disease "characterized by compulsive, at times uncontrollable drug craving, seeking, and use despite devastating consequences—behaviors that stem from drug-induced changes in brain structure and function. These changes occur in some of the same brain areas that are disrupted in various other mental disorders," writes Dr. Nora D. Volkow in the introduction to the report, *Comorbidity: Addiction and Other Mental Illnesses*. "Even though we cannot always prove a connection or causality, we do know that certain mental disorders are established risk factors for subsequent drug abuse—and vice versa."

Surveys show high rates of substance use disorders among people with mental illness. People diagnosed with a mood or anxiety disorder are about twice as likely as others to abuse drugs, and people with schizophrenia have higher rates of tobacco and alcohol use disorders than the general population. For example, 41 percent of mentally ill respondents to the 1991–1992 National Comorbidity Survey said they were current smokers, almost double the rate of those with no mental illness. Other studies indicate that as many as 90 percent of people with schizophrenia smoke.

People who abuse drugs also have high rates of mental illness. By some estimates, about 60 percent of people with drug use disorders have been diagnosed with another mental disorder. A recent clinic-based study of 865 substance abusers found that 66 percent had at least one co-occurring mental disorder (see "Recovery Checkup System Helps Substance Abusers Who Have Mental Disorders," page 4).

The high prevalence of comorbid substance use and other mental disorders does not necessarily indicate that one condition causes the other. According to the report, there are at least three possible explanations for such co-occurring diagnoses:

- Drug abuse may be a risk factor for one or more symptoms of another mental illness. The increased risk of psychosis in some marijuana abusers has been offered as evidence supporting this possibility.
- Some individuals with mental disorders use drugs as a form of self-medication. A common example of this hypothesis is the use of tobacco products by patients with schizophrenia. The nicotine in tobacco may diminish symptoms of the disease, improve cognition, or decrease the side effects of medications.
- Drug abuse and other mental disorders are both caused by common factors, such as underlying brain deficits and early exposure to stress or trauma. For example, brain circuits that use dopamine are typically affected by addictive substances and may also be involved in depression, schizophrenia, and other psychiatric disorders.

All three scenarios are likely to contribute, in varying degrees, to the establishment and expression of specific comorbidity pairings.

DEVELOPMENTAL FACTORS

There is evidence suggesting that early drug use may be a risk factor for the later occurrence of mental illness. The link may hinge upon genetic vulnerability, psychosocial experiences, or a person's environment. Having a mental disorder in childhood or adolescence also increases the risk of drug abuse.

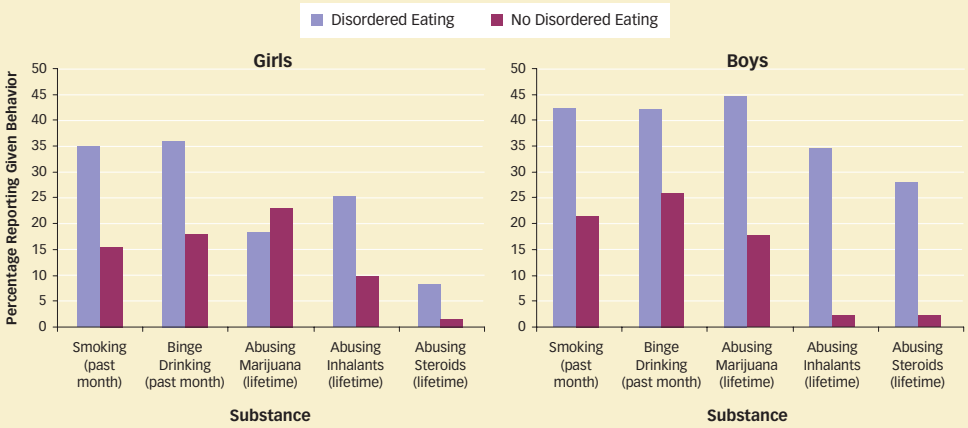
Numerous studies have documented an increased risk for drug use disorders in youth with untreated ADHD; some of these studies suggest that only a subset of these young people—those with co-occurring conduct disorders—are vulnerable. Treatment with stimulants reduces ADHD symptoms and may also reduce the associated risk of drug abuse.

The report stresses the importance of careful and accurate diagnosis and treatment of each disorder. It gives examples of medications and behavioral therapies that have been successful and others that show promise in treating co-occurring disorders.

The full report is available online at *www.drugabuse.gov/researchreports/comorbidity*. ■

WHAT THE NUMBERS SAY

Teens With Unhealthy Weight Control Behavior Are More Likely to Abuse Drugs



High school students who attempt to control weight by engaging in unhealthy behaviors—fasting, purging, or using diet aids without a doctor's advice—are also more likely to have substance abuse problems. Only lifetime marijuana use in girls was lower among those who engaged in unhealthy weight control behaviors. Among the 13,917 teens who participated in the 2005 Youth Risk Behavior Surveillance System, 20 percent of girls and 10 percent of boys reported unhealthy weight control behaviors during the past month.

Source: Pisetsky, E.M. et al. Disordered eating and substance use in high-school students: Results from the Youth Risk Behavior Surveillance System. *International Journal of Eating Disorders* 41(5):464–470, 2008.

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